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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,824	05/27/2005	Kenji Miyazaki	Q88284	1306

23373 7590 09/12/2008

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EXAMINER	
XU, XIAOYUN	

ART UNIT	PAPER NUMBER
1797	

MAIL DATE	DELIVERY MODE
09/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,824	MIYAZAKI ET AL.	
	Examiner	Art Unit	
	ROBERT XU	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/27/2005, 4/5/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

1. This is the initial Office action based on the 10/536,824 application filed on May 27, 2005.

2. Claims 1-14 are pending and have been fully considered.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsugita et al. [Electrophoresis, 1998, Vol. 19, page 928-938] (Tsugita) in view of Tsugita'1992 [Chemistry Letters, 1992, page 235-238] and Vogt et al. [Polymer Bulletin, 1996, Vol. 36, page 549-555] (Vogt).

In regard to Claim 1, Tsugita discloses a procedure for sequencing proteins or peptide from the C-terminal end. The process comprises the steps of; first step, reacting a protein with an 20% acid anhydride in tetrahydrofuran at 60º for 10 min, the N-terminal of the protein is protected by acetylation and an amino acid residue at C-terminal is modified to generate oxazolone (see page 930, right col., 3rd paragraph); second step, allowing oxazolone of the N-terminal protected protein or peptide react with 5% penta-fluoropropionic methyl ester (PFPMe) in methanol at 5º for 15 min to successive release of the C-terminal amino acid (see page 930, right col., 3rd paragraph); finally, allowing the reaction product to react with an amine to hydrolyze the ester (see page 930, right col., 3rd paragraph). The result is analyzed by MALDI-TOF-MS or FAB-MS (see page 931, left col. 2nd paragraph). The method is developed for a protein extracted from polyacrylamide gel as well as for a protein on an Immobilon-CD membrane electroblotted from a polyacrylamide gel (see page 931, left col. 2nd paragraph).

Tsugita uses PFPMe in the second step in the procedure (see page 930, right col., 3rd paragraph); Tsugita also uses perfluoro-alkanoic acid (PFPA) for cleavage at C-side of aspartic acid and the N-side of serine/threonine and simultaneous successive truncation at the C-termini of the cleaved fragments (see abstract). PFPMe and PFPA have similar structure and functions. Tsugita'1992 teaches using PFPA in the second step of the procedure to successively release N-terminal amino acid (see page 236, flow chart). At the time of the invention, it would have been obvious to ordinary skill in the art to use PFPA in the second step of the procedure based on teaching of Tsugita'1992 and Tsugita.

The temperature of 5º used in the second step of Tsugita's procedure is lower than the 30-80º recited in the instant claim. Applicant is advised that generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, it would have been obvious to one of ordinary skill in the art to discover the optimum range of the reaction temperature by routine experimentation.

Tsugita does not teach using dipolar-aprotic solvent to swollen the gel so that the above reaction could be carried out on the protein bound to the original gel right after electrophoresis. Tsugita teaches that the first and second step of the procedure needs to be carried out in the absence of water (page 931, right col. 2nd paragraph, last 2 lines; page 930, 3rd paragraph). Therefore, the target protein has to be extracted from the gel and then dried to remove water or electroblotted to an Immobilon-CD membrane. Vogt teaches a new non-aqueous swelling system that carboxymethyl cellulose (CMC) gel treated with a dipolar aprotic solvent like *N,N*-dimethylacetamide with *p*-toluenesulfonic acid yields a high reactive gel-suspension of the polymer (see abstract). This dipolar aprotic solvent can remove water from the swollen gel in one step (see page 550, 3rd paragraph), thus allows a direct esterification of the hydroxyl group of CMC (see abstract). At the time of the invention, it would have been obvious to one of ordinary skill in the art to use dipolar aprotic solvent to remove water from the gel carrier bound with

the target protein, as taught by Vogt with reasonable expectation that this would allow Tsugita's procedure be carried out on the target protein kept on the gel carrier.

In regard to Claims 2-4, Tsugita teaches that 20% acetic anhydride is used in the first step of the procedure for applying N-acetylation protection to the N-terminal of the protein and for forming oxazolone at C-terminal of the protein and 5% PFPMe is used in the second step to react with oxazolone (page 930, right col. 3rd paragraph). Tsugita does not specifically teach maintaining acetic anhydride in the second step. However, since the function of acetic anhydride is to form oxazolone at C-terminal for perfluoroalkanoic acid to act on in the second step, it would have be obvious to ordinary skill in the art to recognized that maintaining the concentration of acetic anhydride in the second step may benefit the reaction. Since PFPMe can be replaced by PFPA as has been discussed in regard to Claim 1, the ratio of 20% acetic anhydride to 5% PFPA would be 4:1.

In regard to Claim 5, the pH of PFPA is 0.8.

In regard to Claims 6 and 7, PFPA, used by Tsugita'1992 in successive releasing C-terminal amino acid, has 3 carbon atoms linear-chain.

In regard to Claim 8, as has been discussed in regard to Claims 1-4, in light of teachings of Tsugita and Tsugita'1992, the ratio of PFPA (5%) to acetic anhydride (20%) would be 1:4. In the instant Claim, the lower limit is 20:100 or 1:5. Applicant is advised that generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions

of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, it would have been obvious to one of ordinary skill in the art to discover the optimum ratio of perfluoroalkanoic acid to alkanoic acid anhydride by routine experimentation.

In regard to Claim 9, Tsugita teaches that the first and second step of the procedure needs to be carried out in the absence of water (page 931, right col. 2nd paragraph, last 2 lines; page 930, 3rd paragraph). Tsugita'1992 teaches that the target peptide is dried in a small test tube. The tube is placed in a large test tube which contained PFPA in acetonitrile (page 235, last paragraph). The large tube is flame sealed under vacuum. This implies that the reaction is carried out in the test tube where oxygen has been eliminated.

In regard to Claim 10, Tsugita teaches that the final step is to allow the reaction product to react with an amine in aqueous solution to hydrolyze the ester into carboxyl group (see page 930, right col., 3rd paragraph).

In regard to Claims 11 and 12, Tsugita teaches that in the first step, reacting a protein with a 20% acid anhydride in tetrahydrofuran at 60º for 10 min, the N-terminal of the protein is protected by acetylation and an amino acid residue at C-terminal is modified to generate oxazolone (see page 930, right col., 3rd paragraph).

In regard to Claim 13, Tsugita teaches that the method is developed both for proteins extracted from a polyacrylamide gel and for protein on an Immobilon-CD

membrane, electroblotted from a protein spot on the gel (Page 931 left col., 2nd paragraph).

In regard to Claim 14, Tsugita teaches that the products are analyzed by MALDI-TOF-MS or FAB-MS (see page 931, left col. 2nd paragraph).

Conclusion

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Tsugita'2000 [US Patent No. 6,046,053] discloses a process for sequencing protein or peptide from the C-terminal end.

Uchida [US Patent No. 5,521,097] discloses a method of sequencing a protein or peptide by treating the protein or peptide with CF_3-$(CF_2)_n$-COOH, (n is zero or more integer) or its anhydride.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT XU whose telephone number is (571)270-5560. The examiner can normally be reached on Mon-Thur 7:30am-5:00pm, Fri 7:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571)272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

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